Citation:

Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol.* 2005;161(3):239-249.

PubMed ID: 15671256

Study Design:

Prospective cohort study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To investigate the associations of different protein sources with chronic disease and mortality in postmenopausal Iowa women

Inclusion Criteria:

- Completed a 16-page questionnaire mailed in January 1986

Exclusion Criteria:

- Women who were premenopausal at baseline
- Reported a history of cancer other than skin cancer, known heart disease, or known diabetes
- Left 30 or more food items blank
- Had total energy intake less than 600 kcal/day or more than 5,000 kcal/day

Description of Study Protocol:

Recruitment

- Eligible women between the ages of 55 and 69 years were randomly selected from the Iowa driver's license registry.

Design

· 15-year follow-up prospective cohort study from 1986-2000

Blinding used (if applicable)

not described

Intervention (if applicable)

not applicable

Statistical Analysis

- Macronutrients were expressed as a percentage of total energy, and other dietary covariates were energy adjusted by the regression method.
- The distribution of potential confounding and risk factors were examined by quintiles of total protein intake.
- Continuous variables were categorized into quintiles and treated as indicator variables in statistical models following inspection of their relation with each outcome in univariable analysis.
- Risk ratios (RR) and 95 percent confidence intervals (CI) were calculated using Cox regression.
- Survival was modeled as a function of age using as the referent the lowest quintile of protein intake.
- The relation between dietary protein and each outcome was assessed with multivariable-adjusted nutrient density models.

Data Collection Summary:

Timing of Measurements

- In 1986, the questionnaire inquired about factors known or suspected to be related to cancer, including smoking, physical activity, postmenopausal hormone use, alcohol use and anthropometric measurements.
- Baseline diet was assessed with a semiquantitative food frequency questionnaire (SFFQ). The validity and reliability of the SFFQ was documented in reference 18.
- Supplementary questionnaires were mailed in 1987, 1989, 1992 and 1997 to establish vital status and change of address.
- Incident cases of cancer were ascertained through the State Health Registry of Iowa.
- Deceased non-respondents were identified through linkage with the National Death Index.

Dependent Variables

- CHD mortality, cancer incidence and mortality, all-cause mortality

Independent Variables

- Dietary protein

Control Variables

- Known risk factors related to cancer
- Potential dietary confounding factors

Description of Actual Data Sample:

Initial N: 99,826 were randomly selected; N=41,836 (41.9%) responded

Attrition (final N): 29,017 for the analyses indicating 31% dropout rate

Age: Participants were between the ages of 55 and 69 years at baseline in 1986

Ethnicity: older Caucasian women

Other relevant demographics: Whether groups were significantly different on age and education were not described.

Anthropometrics: Whether groups were significantly different on waist/hip ratio and BMI were not described.

Location: Iowa

Summary of Results:

Key Findings

- 4,843 new cancers, 739 CHD deaths, 1,676 cancer deaths and 3,978 deaths from all causes were identified during 15 years of follow up.
- Among women in the highest quintile, CHD mortality decreased by 30% from an isoenergetic substitution of vegetable protein for carbohydrate (95% CI: 0.49, 0.99) and of vegetable for animal protein (95% CI: 0.51, 0.98), following multivariable adjustment.
- Although no association was observed with any outcome when animal protein was substituted for carbohydrate, CHD mortality was associated with red meats (RR=1.44, 95% CI: 1.06, 1.94) and dairy products (RR=1.41, 95% CI: 1.07, 1.86) when substituted for servings per 1,000 kcal of carbohydrate foods.

Author Conclusion:

- Dietary proteins from animal and vegetable food sources appear to be differentially associated with mortality from CHD and all causes when substituted for carbohydrates in the diet.
- Long-term adherence to high-protein diets, without discrimination toward protein source, may have potentially adverse health consequences.

Reviewer Comments:

The dropout rate (31%) is high, and specific follow-up methods of handling withdrawals were not described in this study.

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	No
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	No
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A

3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	No
4.1.	Were follow-up methods described and the same for all groups?	No
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	No
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	No
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A

6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	No
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes

8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes